

**STUDY PROTOCOL****Study of Left Main Coronary Artery Healing after PCI with Boston Scientific  
Synergy Bioabsorbable Polymer Stent****SOLEMN Study (Synergy OCT *LE*ft *MAi*N)**

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**PROTOCOL SIGNATURE PAGE****Study of Left Main Coronary Artery Healing after PCI with Boston Scientific Synergy Bioabsorbable Polymer Stent****SOLEMN Study (Synergy OCT *LE*ft *MAi*N)**

I have read this protocol, appendices and amendment(s), if applicable, and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the device and the conduct of the study.

I will conduct the study in accordance with the protocol and Good Clinical Practice guidelines, as well as local regulations, and I accept respective revisions to the protocol approved by authorized personnel of the Sponsor and by regulatory authorities.

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Primary Investigator (print)

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Primary Investigator (signature)

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Date

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## 2. SPECIFIC AIMS

### 2.1. Background

Percutaneous coronary intervention (PCI) is increasingly used to treat unprotected left main (LM) coronary artery stenosis.(2) Both protected and unprotected LM PCI are considered standard of care in most centers worldwide and in the United States. and LM PCI has been associated with favorable outcomes compared to CABG.(3-5)

### 2.2. Challenges of Left Main Stenting/PCI

However, due to its critical location, stent failure in LM PCI is of particular concern. Specifically, stent thrombosis (ST) in this location is associated with adverse outcome.(6) Improvement in stent design and introduction of newer generation drug-eluting stents has reduced occurrence of ST.(7)

The Boston Scientific Synergy™ stent is a new generation bioabsorbable polymer drug-eluting stent (BP-DES) with thinner struts (2.25-2.75mm - 74µm, 3.0-3.5mm - 79 µm and 4.0mm - 81µm) and an abluminal thin coat of bioabsorbable polymer which is fully absorbed over a period of 3 months along with the elution of the anti-restenotic drug everolimus. These technical characteristics promote a more complete and quick healing process with the

Synergy™ stent as it has been shown in previous studies.(8)

### 2.3. OCT detection of stent strut coverage

Optical Coherence Tomography (OCT) allows for precise determination of stent placement, stent expansion and apposition.(9, 10) The pattern of vessel healing can be very precisely studied,(11) in particular when immediate post-stent implantation OCT data is compared to the 3- or 6-month post-PCI intervals.(8, 12) OCT-guided PCI is associated with improved outcome (as measured by Fractional Flow Reserve – FFR) in high-risk NSTEMI patients without increasing periprocedural complications.(13)

Optimal and consistent vessel healing is particularly important in LM PCI where stent thrombosis is a potential complication with serious adverse outcome.(6) In the recent PESTO trial, OCT identified the underlying morphological abnormality in 97% of cases of ST. There were multiple underlying mechanisms identified - strut malapposition, ruptured neoatherosclerosis, and severe underexpansion.(14) Imaging-guided PCI in LM PCI (e.g., IVUS) has been associated with improved outcomes.(15) Similarly, the CLI-OPCI study demonstrated that suboptimal stent deployment as visualized by OCT was associated with increased MACE.(9)

### 2.4. Left Main imaging as surrogate endpoint for clinical trial

Full stent coverage has been associated with reduced MACE and improved outcomes.(16) Similarly, ST is felt to be reduced with full stent strut coverage. Since contemporary drug-eluting stent, in particular BP-DES may afford faster and more complete healing(17) it has been suggested that stent strut coverage may be used, in certain domains of care, as a surrogate marker of full stent healing and be associated with shortened DAPT duration.

Temporal trends in stent strut coverage suggest that newer generation drug-eluting stents have faster stent healing/coverage approaching those observed with bare-metal stents.(18) Since shorter DAPT duration is feasible and in routine clinical use with BMS we feel that stent strut coverage may be, at least in part, be used as a surrogate marker for a clinical trial investigating Synergy stent healing.(19, 20)

### 2.5. Hypothesis

Our main hypothesis is that the healing patterns in LM will be favorable (full and rapid strut coverage) with the use on the BP-DES.

Due to the gradual disappearance of the bioabsorbable polymer (BP) on the Boston Scientific Synergy™ stent over time, early strut coverage patterns and timeline may be different than previously observed in durable polymer (DP) drug-eluting stents (DES) and bare-metal stents (BMS) stents in LM PCI.(21, 22)

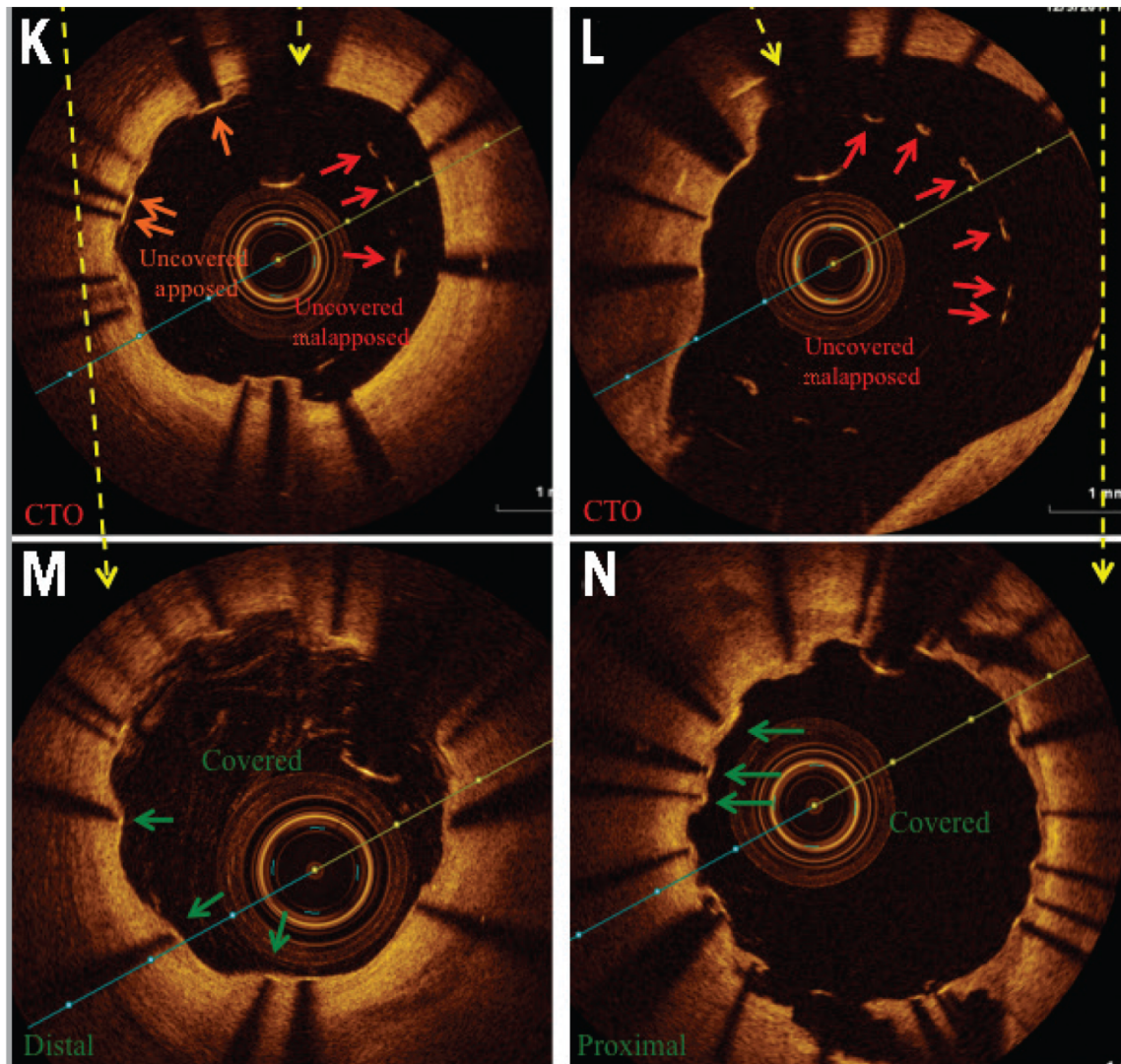
Late acquired stent malapposition (LASM) is expected to differ from previous observations with DP DES.(23, 24)

The unique attributes of the BP technology present on the Synergy™ stent may potentially allow for reduction in the duration of the dual antiplatelet therapy (DAPT) following LM PCI. BP-DES have been shown to have superior clinical outcomes compared to BMS and first-generation DES, while outcomes were similar to DP second-generation DES.(25) Therefore, this new information about stent healing process with BP-DES is particularly important given the critical location of LM PCI procedure.

Additionally, our study will include all-comers, unprotected and protected LM PCI allowing for assessment of differences in neointimal hyperplasia (NIH) in LAD and LCX.(26)

The additional risk of this study to patients is small given the demonstrated safety of OCT.(13) Both angiographic and follow-up has been routinely performed in multiple studies and has demonstrated safety in previous studies.(27, 28) Therefore, performance of 3- and 12-month follow-up in this study of healing of LM is an accepted clinical and research practice.



**Figure 1.****Unapposed stent struts post PCI(1)****2.6. Specific Aims**

We expect to observe early and complete healing of the BP-DES Synergy stent in the LM position and a very low percentage of malapposed struts.(8) In addition, we expect to observe significant reduction of neointimal hyperplasia.

**3. RESEARCH PLAN**

### 3.1. Trial, Site and Data Infrastructure

The Department of Veterans Affairs (VA) is the single largest integrated healthcare system in the US. The recent national approval and introduction of the Boston Scientific Synergy Stent at the VA provides a unique opportunity to perform a prospective observational study of this device.

The VA operates an advanced Electronic Medical Record (EMR) that is consistent across the whole system, and Clinical Assessment Reporting and Tracking (CART) system used by all VA cardiac catheterization laboratories.(29) VA offers robust follow greater than 85% of its patients within its own healthcare system.(30)

Additionally, the VA serves a highly complex population with significant CAD and multiple co-morbidities. This environment is particularly well-suited with performance of this trial.

### 3.2. VA Procedure Volume (2014)

- 78 VA Cardiac Catheterization Laboratories nationwide
- 37,813 patients with 39,464 diagnostic coronary angiographies
- 11,013 patients with 12,248 PCIs

### 3.3. VA PCI Characteristics (2014)

- Indications

Stable Angina	33%
Unstable Angina	27%
NSTEMI	23%
STEMI	7%

- Arterial Access

Femoral	75%
Radial	25%

### 3.4. Anticipated VA Study Sites

VA Site	Principal Investigator
San Francisco	Kendrick Shunk
Oklahoma City	Faisal Latif
Minneapolis	Edward Mcfalls
Pittsburgh	Aref Rahman

Atlanta	Kreton Mavromatis
San Antonio	Robert Chilton
Cleveland	Noah Rosenthal
Dallas	Subhash Banerjee
Chicago	Mladen Vidovich
Tucson	Tam Truong
Long Beach	Arnold Seto
Birmingham	Masood Leesar
Denver	Ehrin Armstrong
Charleston	Valerian Fernandes

### 3.5. Core Laboratory Experience

The Clinical Trials Center (CTC) at the Cardiovascular Research Foundation (CRF) has contributed to key advances in interventional cardiovascular disease. Through the design and execution of clinical trials, the CTC has played a pivotal role in bringing innovative new technologies, pharmacologic therapies, and new treatment paradigms to patients. Led by thought leaders in clinical research and practice, the CTC is uniquely positioned to design clinical research protocols that answer the most important questions in cardiovascular medicine. Drawing upon a thorough understanding of treatment guidelines, as well as the research and regulatory landscape, the CTC works with sponsors to design and execute studies that have a profound impact on patient care. The CTC has been involved in more than 650 clinical studies with enrollment of over 150,000 subjects, including seminal trials that have shaped the field. This high-quality portfolio draws small startups, as well as large companies, that seek the expertise, passion for innovation, and quality of CRF.

## 4. RESEARCH DESIGN AND METHODS

### 4.1. Experimental Design

The proposed study is a multicenter, observational, prospective, single-arm study of stent strut coverage of patients undergoing LM PCI.

Baseline quantitative coronary analysis (QCA) will be performed at the time of stent implantation.

Stent coverage in LM PCI will be studied with OCT at 3 and 12 months and compared to baseline OCT at the time of stent implantation.(31, 32)

OCT/data will be analyzed in a core lab (CTC CRF) and correlated with clinical outcomes at 3 and 12 months.

#### 4.2. Primary Endpoint

- 3-month stent strut coverage in LM PCI

#### 4.3. Secondary Endpoints

- 12-month stent strut coverage in LM PCI
- 3-month late acquired stent malapposition (LASM)
- 12-month late acquired stent malapposition (LASM)
- One-month LM Synergy stent safety
- 1-, 3- and 12-month MACE
- 1-, 3- and 12-month Stent Thrombosis (ST) (ARC definition)

## 5. STUDY POPULATION

75 patients undergoing LM PCI (protected or unprotected) with Boston Scientific Synergy™ stent.

The goal is to enroll 75 patients from up to 10 VA sites and an enrollment period of 3 years, each site is expected to include 7-10 patients during the study period.

After a total of 75 patients are enrolled the study will be closed for further enrollment.

Eligible patients will be screened at each participating center and those who had undergone LM PCI with Boston Scientific Synergy™ stent and where OCT was performed during the index procedure will be eligible. The index procedure may be performed by any interventional cardiologist – this is specifically needed in order to maintain equipoise on the part of stent choice and use of OCT.

At the end of the study enrollment period, the proportion of patients at each site treated with Synergy stents vs. non-Synergy stents and the proportion of patients that underwent OCT imaging during LM PCI will be collected.

Eligible patients will be approached and consented for inclusion in the SOLEMN trial after the initial procedure.

#### 5.1. Collection of Race and Ethnicity Data

Race and ethnicity will be collected via the CRF at the time the patient is enrolled in the trial. For example, several studies have shown that South Asians in North America have a higher burden of cardiovascular disease and cardiovascular deaths compared to whites and other ethnic groups.(33) Similarly, there are differences in cardiovascular outcomes after revascularization in women or different ethnicities.(34)

The Department of Veterans Affairs population which can be considered for the trial consists mainly of male subjects. The ethnic background can vary considerably between various sites. Previous studies performed at the VA have therefore reported inclusion of populations that may not fully represent the US population as a whole. For example, a large VA-sponsored Cooperative Trial (PRESERVE) enrolled >90% of a male population which was almost 80% white.(35)

Therefore, while the study investigators will maintain records and document gender, race and ethnicity, the SOLMEN trial will likely consist of a population specific to the environment present at the Department of Veterans Affairs Hospitals. These are recognized limitations of all trials performed within the Veterans Affairs environment.

### 5.2. Randomization and blinding

This is in single arm study with no randomization or blinding.

### 5.3. Study Duration

Patients will be followed for 12 months after the index procedure. At one month, clinical follow-up will be performed (clinic or telephone). At 3 months, the angiography and OCT will be performed. At 12 months, the final angiography and OCT will be performed. No further follow-up is planned after completion of the 3- and 12-month angiography and OCT.

### 5.4. Patient Withdrawal

Each patient is free to withdraw from the study at any time and without reason, and without influence on their further medical treatment or relationship to their physicians. Once the patient is withdrawn, they will be followed per institutional standard of care.

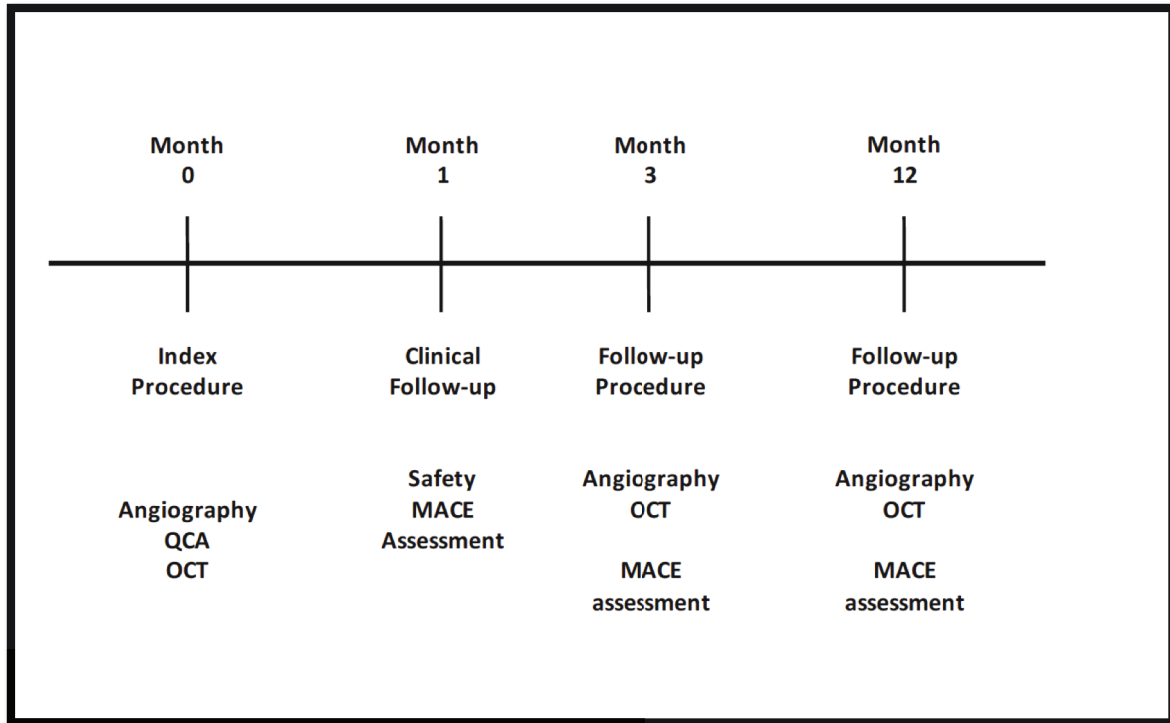
## 6. PRE- AND POST-PROCEDURE FOLLOW-UP ASSESSMENTS

Baseline, procedure and follow-up assessments will be performed according to the schedule described in Figure 2. "Flowchart of the study design". During each specified evaluation, the corresponding Case Report Form (CRF) must be completed.

Subject telephone numbers should be obtained to ensure contact is maintained. These telephone numbers should include all home numbers, work numbers as well as primary physician numbers. A phone number of a relative or friend should also be requested.

**Figure 2.**

Flowchart of the study design.



### 6.1. Baseline Data

Every patient will undergo baseline assessment as outlined below.

- Baseline demographics and clinical characteristics will be recorded as outlined in the case report form.
- Medications
- Laboratory studies including complete blood count, basic metabolic panel, lipid panel and glycosylated hemoglobin (HgbA1C).
- Electrocardiogram

### 6.2. Hospital Discharge

- Clinical assessment and physical exam, including angina status;
- CBC;
- Serum creatinine;
- 12-lead ECG

- Post-procedure 12-lead ECG: an ECG should be performed between 12 – 24 hours post-procedure or prior to discharge if less than 12 hours;
- Record of all cardiovascular medications, including DAPT and anti-coagulants
- If the patient enrolled had NSTEMI during the index procedure, documentation that the cardiac enzymes were stable and declining at the time of the index procedure. No additional biomarker follow-up as part of the SOLEMN trial is required.
- The corresponding Hospital Discharge Case Report Form (CRF) must be completed;
- Cardiac Catheterization and Percutaneous Coronary Intervention Report(s) for the Index Procedure.
- Coronary Angiograms (DICOM)
- OCT Imaging (St. Jude format)

#### 6.3. 1 month (plus or minus 2 weeks)

- Telephone assessment or clinic visit;
- The corresponding 1-month Case Report Form (CRF) must be completed;
- Record of all cardiovascular medications, including DAPT and anti-coagulants;
- Record of all adverse events

#### 6.4. 3 Months (plus or minus 1-month)

- Repeat coronary angiography and LM OCT;
- The corresponding 3-month Case Report Form (CRF) must be completed;
- Record of all cardiovascular medications, including DAPT and anti-coagulants;
- Record of all adverse events;
- ECG;
- CBC and serum creatinine.
- Cardiac Catheterization and, if clinically indicated, Percutaneous Coronary Intervention Report(s)
- Coronary Angiograms (DICOM)
- OCT Imaging (St. Jude format)

#### 6.5. 12 Months (plus or minus 1-month)



- Repeat coronary angiography and LM OCT
- The corresponding 12-month Case Report Form (CRF) must be completed
- Record of all cardiovascular medications, including DAPT and anti-coagulants;
- Record of all adverse events; and
- ECG;
- CBC and serum creatinine;
- Cardiac Catheterization and, if clinically indicated, Percutaneous Coronary Intervention Report(s)
- Coronary Angiograms (DICOM)
- OCT Imaging (St. Jude format)

### 6.6. Additional Visits

Under certain circumstances, the Sponsor or Investigator may request an evaluation of the Subject either before or after a scheduled visit, i.e., an additional visit. If an additional follow-up is due to concern over a suspected adverse event or a suspected device deficiency, the visit must be documented as an additional visit.

If the Subject experiences a cardiac event (i.e., Non-STEMI or STEMI) or complains of other new or unresolved signs or symptoms, an additional visit is required to be documented and reported as an adverse event. It is the discretion of the Investigator to determine other assessments and treatment methods for an additional visit.

Data collected at additional visits includes date and reason of follow-up, assess for adverse events and any study activities performed.

### 6.1. OCT Data and Clinical Interventions

Since the benefit of follow-up LM OCT has not been established, we will collect data how the operators used the additional imaging data obtained during the patient participation in the SOLEMN study.

## 7. POST-PROCEDURE ANTI-PLATELET MEDICATION

### 7.1. Aspirin



Following PCI, subjects with no known aspirin allergy or bleeding risk should continue on aspirin (minimum of 75 mg/day up to 162 mg/day or dose per standard hospital practice) indefinitely.

## 7.2. Additional Antiplatelet Therapy

6-month minimum of DAPT (Dual Antiplatelet Therapy) duration is recommended in the SOLEMN trial.

Subjects should be treated in accordance with current US guidelines. All cardiovascular medications will be recorded for data collection at each visit. Please refer to the specific package insert for the designated P2Y12 medication e.g., Clopidogrel, Ticlopidine, Ticagrelor or Prasugrel for indications, contraindications, warnings and precautions.

### SCHEDULE OF EVENTS

PROCEDURE/TEST	Index Procedure	Screening and Baseline	30 Days	3 Months	12 Months
Visit Number	-	1	2	3	4
Range from the index procedure	-	+ 1-2 Days	+/- 14 Days	+/- 30 Days	+/- 30 Days
Informed Consent Form		X			
12-lead ECG		X		X	X
Demographics and Medical History		X			
General Clinical State		X	X	X	X
CBC, Serum creatinine		X		X	X
Troponin I		X		X	X
Coronary Angiogram (DICOM)	X			X	X
LM OCT Imaging (St. Jude format)	X			X	X
Cardiac Medication Profile		X	X	X	X

Deviations, Adverse Events		X	X	X	X
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## 8. SUBJECT RECRUITMENT & SELECTION CRITERIA

Patients who have undergone clinically-indicated PCI of LM where OCT was performed as part of the routine index procedure will be identified by a local study investigator or study coordinator and will be screened for eligibility for the study. Only patients who have already undergone LM PCI and OCT as part of routine, standard care will be approached.

The index LM PCI procedure may be performed by *any* operator regardless of their participation in the SOLEMN study.

The follow-up procedures can be performed by SOLEMN investigators only.

The following criteria will be used:

### Inclusion criteria:

- Age 18 years or greater;
- Left Main CAD, defined as  $\geq 50\%$  diameter stenosis and amenable to revascularization by PCI;
- Willing and able to give informed consent. The patients must be able to comply with study procedures and follow-up.
- Ability to comply with minimum of 6 months of DAPT after the index procedure.
- Unprotected Left Main PCI
  - a. The IFU for Dragonfly OPTIS Imaging Catheter indicates that the catheter is contraindicated for use in patients disqualified for CABG surgery. The patients in the SOLEMN trial will have had OCT performed with their LM PCI prior to enrollment. The decision to perform unprotected LM PCI therefore will have been made prior to enrollment in the SOLEMN trial. The initial indication to perform LM PCI and LM OCT is at the discretion of the interventional cardiologist prior to enrollment into the SOLEMN trial. The SOLEMN trial will not allow for enrollment of patients who are disqualified for CABG surgery.
- Protected Left Main PCI
  - a. The IFU for Dragonfly OPTIS Imaging Catheter indicates that it is intended for use in vessels 2.0 – 3.5 mm in diameter. The SOLEMN

trial specifically allows for imaging of LM vessels that are larger in diameter.

- b. The IFU for Dragonfly OPTIS Imaging Catheter specifies that it is not intended for use in the left main coronary artery or in a target vessel which has undergone a previous bypass procedure. The SOLEMN trial specifically allows for imaging of protected/bypassed LM and/or into the LAD or LCX, as appropriate.

#### Exclusion criteria:

1. Coexisting conditions that limit life expectancy to less than 12 months or that could affect patient's compliance with the protocol;
2. Serum creatinine greater than 2.0 mg/dL;
3. Cardiogenic shock;
4. STEMI;
5. Non-STEMI, if the cardiac troponin is not stable or starting to decline;
6. Pregnancy;
7. Inability to take dual antiplatelet therapy for 6 months;
8. Any target lesion with previously placed stent.
9. Patients disqualified for CABG surgery.

#### Contraindications for OCT use:

1. Bacteremia or sepsis
2. Major coagulation system abnormalities
3. Severe hemodynamic instability or shock
4. Patients diagnosed with coronary artery spasm
5. Acute renal failure

The study design will be explained to the patients and if they agree to participate and they will be asked to sign in the consent form and they will receive a copy of the consent form.

## 9. BENEFITS AND RISKS

### 9.1. Benefits

- Left main PCI has been widely used as an alternative to CABG in selected patients with symptomatic coronary artery disease. The potential benefits of the Boston Scientific Synergy™ stent are the low profile, improved flexibility and bioabsorbable nature of the polymer. The positive clinical outcomes seen from the global and United States experience have

demonstrated that the stent is safe and effective in a wide range of applications in the coronary tree.

- Optical coherence tomography has been widely used in the coronary arteries and has demonstrated exceptional resolution and detail when studying native coronary artery disease as well as healing of the metallic stent implants. Multiple studies of OCT have demonstrated its reproducibility and safety across variety of lesions, anatomies and coronary locations.

## 9.2. Risks

- The risk assessment and management was performed per the ISO EN 14971 Standard According to the Medical Device Classification (Medical Device Directive 93/42/EEC, Rule 13 Annex IX) and Code of Federal Regulations (21CFR860.3), the Boston Scientific Synergy™ stent is a Class III device, long-term implantable medical device incorporating integral medicinal product liable to act in ancillary way on human body.
- As described previously, the potential benefit of the Boston Scientific Synergy™ stent in the left main coronary artery are its flexibility, thin-strut design and bioabsorbable polymer. Potential risks are all that apply to implantation of a drug-eluting stent, placement of the stent in left main coronary artery and the fact that Boston Scientific Synergy™ stent has not been studied in the left main coronary artery. This study is specifically not designed to seek approval of Boston Scientific Synergy™ stent in the left main coronary artery. Instead, it is the study of healing of the Boston Scientific Synergy™ stent in this location.
- Other risks associated with using this device are those associated with percutaneous treatment procedures for a stenotic coronary artery. The complications relating to standard PTCA and stenting include, but are not limited to the following:
  - Abrupt stent closure
  - Abrupt vessel closure or spasm
  - Acute myocardial infarction
  - Allergic reaction to anti-coagulation and/or anti-thrombotic therapy, contrast material, or stent and/or delivery system materials
  - Aneurysm, pseudo aneurysm, or arteriovenous fistula
  - Arrhythmias (including ventricular fibrillation and ventricular tachycardia)
  - Cardiac tamponade
  - Cardiogenic shock
  - Death

- Damage to the stent or injury to the artery requiring emergency coronary artery bypass grafting (CABG)
  - Dissection, perforation, or rupture of the coronary artery
  - Emboli (blockage), distal (air, tissue or thrombotic emboli)
  - Fever
  - Hematoma at catheter insertion site
  - Hemorrhage requiring transfusion
  - Hypotension / hypertension
  - Increased risk of restenosis of stented segments
  - Infection and/or pain at catheter insertion site
  - Perforation or rupture of the artery
  - Peripheral ischemia / peripheral nerve injury
  - Renal failure
  - Stent migration or embolization
  - Stent thrombosis or occlusion
  - Stroke or transient ischemic attack
  - Total occlusion of coronary artery
  - Unstable angina
- As mentioned above, there are also potential risks that may be associated with implantation of Boston Scientific Synergy™ stent which may include, but are not limited to the following:
    - Allergic/ immunologic reaction to drug
    - Alopecia
    - Anemia
    - Blood product transfusion
    - Chest Heaviness
    - Dizziness
    - Gastrointestinal symptoms
    - Headache
    - Hematologic dyscrasia (including Leukopenia, Neutropenia, Thrombocytopenia)
    - Hepatic enzymes change
    - Histological changes in vessel wall, including inflammation, cellular damage or necrosis
    - Lymphadenopathy
    - Mouth Ulcers
    - Myalgia/Arthralgia
    - Nausea
    - Peripheral Neuropathy
    - Skin Rash
  - The occurrence of the above listed complications may lead to the need for a repeat catheterization and/or percutaneous coronary intervention, myocardial infarction, stent thrombosis, stroke, emergency bypass

surgery, or death. The risks associated with the Boston Scientific Synergy™ stent are believed to be similar, although possibly less due to the bioabsorbable nature of the polymer, to those risks associated with second generation drug eluting stents currently in use to treat a stenotic coronary artery. Additional risks, which are not known at this time, may also exist. Appropriate contraindications and warnings are included in the Instructions for Use (IFU).

### 9.3. Optical Coherence Tomography (OCT)

- The C7 Dragonfly, Dragonfly DUO, or Dragonfly OPTIS Imaging Catheter is not intended for use in the left main coronary artery. Currently, the catheter is being used clinically for left main imaging in the United States and globally. This study is not designed to seek approval of use of the OCT catheter in the left main coronary artery. Additional risks of OCT, which are not known at this time, may also exist. Appropriate contraindications and warnings are included in the Instructions for Use (IFU).
- The following complications have been described with the use of Optical Coherence tomography catheters:
  - Coronary artery spasm
  - Unstable angina
  - Allergic reaction to the contrast media
  - Kidney damage due to contrast media
  - Arterial dissection, injury or perforation
  - Thrombus formation, abrupt closure or total vessel occlusion
  - Abnormal heart rhythms
  - Embolism
  - Acute myocardial infarction
  - Death
  - Catheter entrapment

## 10. TREATMENT

### 10.1. Arterial Access Site

- Follow-up PCI can be performed via the radial artery or the femoral artery, as per the site's usual routine.

### 10.2. Follow-up assessments: 3 months and 12 months

The follow-up assessments at 1, 3 months, and 12 months include:

- Patient status and any adverse events;
- A clinical assessment and physical examination;
- Complete Blood Count (CBC)
- Serum Creatinine
- Cardiac enzymes
- Record of all medications
- Angina status
- Any medical care received

### 10.3. MACE Definition

- MACE (Major adverse cardiac events) will be defined as cardiac death, nonfatal myocardial infarction, or target lesion revascularization.

## 11. ANGIOGRAPHY, PCI AND OCT

### 11.1. Baseline angiography and PCI

- Baseline angiography and PCI will be performed as per clinical routine at each participating center. Adjunctive pharmacologic therapy during and immediately after the PCI should be prescribed as per the clinical routine at each participating center.
- Only patients with PCI performed with Boston Scientific Synergy™ stent will be eligible for the trial.
- Covering the entire diseased portion of the lesion with a single drug-eluting stent is recommended.
- Left main bifurcation strategy will be performed per clinical routing at each participating center (e.g., culotte, crush, DK-crush, TAP, etc.).

### 11.2. Baseline and follow-up OCT

#### Performance of OCT

- OCT should be performed with the St. Jude OCT system. For correct use of the OCT catheter and the St. Jude recording system, refer to the instructions for use provided by St Jude Medical along with the product.
- Ensure correct calibration of all equipment.
- In order to obtain high-quality images, it is strongly advocated to use power injection due to the large caliber of the LM and presence of high flow.

### 11.3. Follow-up 3- and 12-month Angiography

For angiographic assessment,  $\geq 2$  unforeshortened views of the LM with angiographic projections  $>30$  degrees apart from one another should be obtained at the time of 3- and 12-month follow-up procedure(s). It is recommended that at follow-up angiography,  $\geq 2$  unforeshortened views of the lesion identical to the index procedure be obtained. It is recommended that the images be acquired at 15 to 30 frames per second.

### 11.4. OCT Methodology

After adjusting for the pullback speed, cross-sections will be analyzed at 0.6-mm longitudinal intervals throughout the treated segment. Lumen contours will be traced using semiautomatic algorithms. Detection of metallic stent struts will be performed automatically with manual adjustments made as necessary. Stent area tracings will be automatically performed by interpolated contours connecting the center point of the luminal surface of each detected metallic strut. Stent expansion will be determined as the minimum stent area divided by the average reference lumen area and presented as a percentage. The stent eccentricity index will be calculated in every analyzed cross-section as  $(\text{maximum stent diameter} - \text{minimum stent diameter}) / \text{maximum stent diameter}$ . Neointimal hyperplasia (NIH) area will be determined in follow-up examinations as the area between the stent and lumen contours. The percentage of NIH obstruction of the stented area will be automatically determined in each analyzed cross-section at follow-up as  $(\text{NIH area} / \text{stent area}) \times 100$ . Incomplete stent apposition (ISA) area will be determined as the area between the stent contour and the lumen contour at the site of malapposed struts, in a region not overlying a side branch ostium. ISA volume will be automatically computed by the Simpson rule.

At the strut level, the strut-to-lumen distance will be automatically measured from the center point of the luminal surface of each analyzed strut to the lumen contour by a line projected through the gravitational center of the lumen. Covered struts will be considered when they have positive strut-to-lumen distances, a measure of the NIH thickness covering each strut. Uncovered and malapposed struts will be considered when they have negative strut-to-lumen distances. Malapposed struts will be differentiated from uncovered struts when the negative value of the strut-to-lumen distance is higher than the sum of the strut thickness + a compensation factor of  $20 \mu\text{m}$  to correct for the strut blooming.<sup>(36)</sup> Thus, a cutoff of  $101 \mu\text{m}$  ( $74$  or  $79 \mu\text{m}$  for strut thickness +  $20 \mu\text{m}$  for the compensation factor) will be used for determination of stent strut malapposition. The ratio of uncovered to total stent struts (RUTTS) will be calculated in each analyzed cross-section as the number of uncovered struts divided by the total number of struts in that particular cross-section. The number of cross-sections in which the RUTTS was  $>30\%$  will be reported for each time point.<sup>(16)</sup>



### 11.5. Single LM Stent OCT

For single-stent LM technique it is anticipated to perform imaging of the whole length of the stent. If the stent is extending into the LAD or LCX the stented segment will be imaged, respectively.

### 11.6. Bifurcation LM Stent OCT

All bifurcation techniques are allowed in the SOLEMN trial. One- and two-stent techniques are allowed. At present time, there are few studies describing OCT of LM and bifurcation of LM and these have described a variety of measurement methodologies.(37-40)

If the index procedures included OCT imaging of both limbs of the LM bifurcation it is recommended that repeat 3- and 12- month OCT imaging be performed to allow for strut coverage comparison.

OCT measurements will be performed by:

- 1) Conventional analysis of the main branch pullback;
- 2) Conventional analysis of the side branch pullback; and
- 3) If available, 3D OCT reconstruction of the bifurcation will be analyzed.

### 11.7. Quantitative Coronary Angiography (QCA) analyses

QCA analyses will be performed at CRF.

### 11.8. Optical Coherence Tomography analyses

OCT analyses will be performed at CRF.

### 11.9. OCT Definitions

The Indications for Use statement in the labeling for the Dragonfly OPTIS image catheter indicates that the device is not intended for use in the left main coronary artery. Therefore, the use of the Dragonfly OPTIS catheter in the SOLEMN study will be considered an off-label use. Multiple previous studies have described protocols for assessing stent strut coverage outside of LM (see below). The SOLEMN protocol allows enrollment of patients who underwent single LM stent placement and any or the currently accepted LM/LAD/LCX bifurcation strategies. Therefore, the OCT Stent Strut Coverage definitions previously described in non-LM vessels (see below) will be used in the SOLEMN trial.

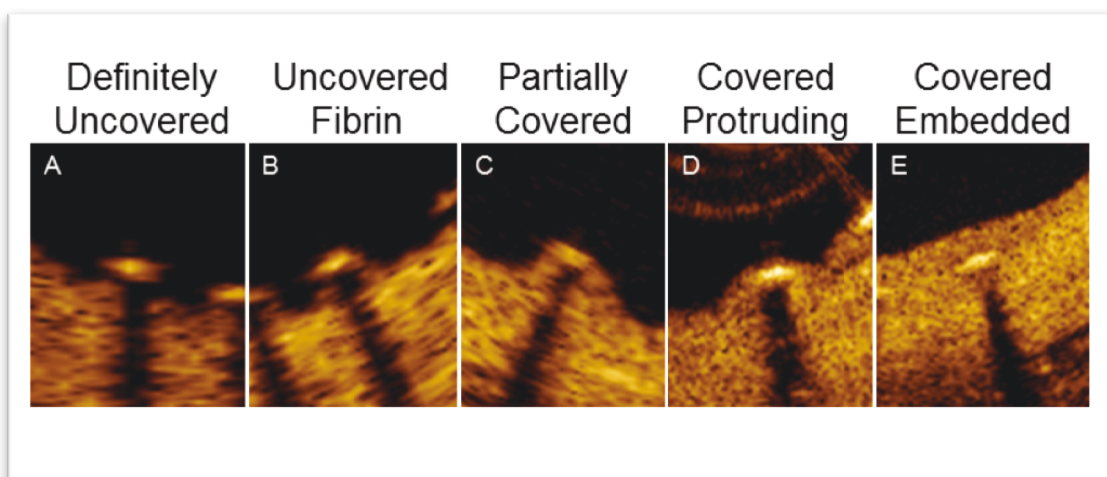
### 11.10. OCT Strut Coverage (Figure 2.)

Strut coverage will be categorized into A-E. D or E will be considered to be covered struts:

- **A=definitely uncovered** - defined as a strut not covered by tissue and both sides appear squared
- **B=uncovered with tissue** - defined as a strut covered by irregular tissue and both sides appear squared
- **C=partially uncovered** - defined as a strut covered by tissue partially and at least one side having a smooth shoulder;
- **D=protruding covered** - defined as a strut covered by tissue, but extending into the lumen
- **E=embedded covered** - defined as a strut covered by tissue and not interrupting the smooth lumen contour.

**Figure 3.**

Classification of Strut Coverage



### 11.11. OCT LASM (Late Acquired Stent Malapposition)

**Malapposition:** Distance from the center of the blooming artifact to the nearby endoluminal surface of the intima will be measured.

Malapposition will be defined as a measured distance greater than the total thickness of the stent metal plus polymer of the stent.

**LASM** (Late Acquired Stent Malapposition) defined as a malapposition visible only at follow-up by comparing follow-up to baseline OCT image

### 11.12. Proposed OCT Measurements

	Index Procedure	3-month f/u	12-month f/u
Post-PCI			
Cross-sectional level analysis			
Mean lumen area (mm <sup>2</sup> )			
Minimal lumen area (mm <sup>2</sup> )			
Mean stent length (mm)			
Intrastent prolapse			
Strut level analysis			
Number of stent strut			
Malapposition			
Follow-up			
Cross-sectional level analysis			
Mean lumen area (mm <sup>2</sup> )			
Minimal lumen area (mm <sup>2</sup> )			
Mean stent length (mm)			
Mean NIH area (mm <sup>2</sup> )			
Percentage of neointimal volume obstruction (%)			
Cross Section with any uncovered strut			
Cross Section with uncovered strut > 0.3			
Cross Section with any malapposed strut			
Presence of thrombi			
Strut level analysis			
Number of stent strut			
Mean Neointimal Thickness (μm)			
Uncovered strut			
Malapposed strut			
Both of malapposed and uncovered strut (%)			

## 12. SAFETY EVALUATIONS

### 12.1. Reporting of Adverse Events

Trial personnel must report to the Jesse Brown Central site any adverse event within 24 hours of learning of the event. The notification can be performed via e-mail, fax or phone. Evidence of the initial notification should be captured. Study personnel must forward follow-up information and the completed adverse event CRF to the Jesse Brown Central site as the event continues and/or resolves. It is the responsibility of the Site Principal Investigator to inform the Institutional Review Board (IRB) of the adverse event as required by local procedure.

- Safety of the subjects participating in this clinical trial will be monitored throughout the trial using the Adverse Event reporting process to identify real and potential safety issues.

### 12.2. Definitions of Adverse Events

#### 12.3. Adverse Event (AE)

- Any untoward medical occurrence, unintended disease or injury or untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device.

#### 12.4. Adverse Device Event (ADE)

- Adverse event related to the use of an investigational medical device.

#### 12.5. Serious Adverse Event (SAE)

- An adverse event that:
  1. led to a death,
  2. led to a serious deterioration in the health of the subject that either resulted in:
    - a) a life-threatening illness or injury, or
    - b) a permanent impairment of a body structure or a body function, or
    - c) in-patient or prolonged hospitalization, or

d) medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.

#### 12.6. Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

#### 12.7. Unanticipated Serious Adverse Device Effect (USADE)

A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

#### 12.8. Unanticipated Adverse Device Effect

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the risk analysis report, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

#### 12.9. Device Deficiency (DD)

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Note: Device deficiencies include malfunctions, use errors, and inadequate labeling.

#### 12.10. Device Malfunction

Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP.

### 13. BIOSTATISTICAL CONSIDERATIONS

#### 13.1. Primary Endpoint Analysis

The primary endpoint is 3-month stent strut coverage and is specifically defined as *Percentage of Uncovered Stent Struts*. The Percentage of Uncovered Stent Struts is the number of struts without distinct overlying tissue, in which the luminal reflection of the strut surface is directly interfacing with the lumen, divided by total number of analyzable struts.

The null and alternative hypotheses for the primary endpoint are:

$H_0: \mu S3 \geq 0.90$

$H_1: \mu S3 < 0.90$

where  $\mu S3$  is the mean percentage of uncovered stent struts for Synergy DES at 3 months after index procedure.

The one-sided significance level of 0.05 will be used.

Baseline clinical characteristics will be analyzed on the patient level whereas OCT data will be analyzed on per-patient, per-lesion, per-segment, and per-strut levels.

Categorical variables will be compared with the  $\chi^2$  or the Fisher exact tests.

Continuous variables will be compared with the 2-sample Wilcoxon rank-sum test.

For segmental and strut analyses, continuous variables will be compared using generalized estimating equations with exchangeable correlation to account for the clustering of values within each lesion and subject.

### 13.2. Secondary Endpoint Analyses

The secondary endpoint or 12-month stent strut coverage and is similarly defined as primary endpoint as defined as *Percentage of Uncovered Stent Struts*. The Percentage of Uncovered Stent Struts at time 0, 3-months and 12-months will be compared with ANOVA.

The additional secondary endpoints (categorical and continuous) will be analyzed as indicated above.

- 3-month late acquired stent malapposition (LASM)
- 12-month late acquired stent malapposition (LASM)
- One-month LM Synergy stent safety
- 1-, 3- and 12-month MACE
- 1-, 3- and 12-month Stent Thrombosis (ST) (ARC definition)

### 13.3. Expected treatment effect

We expect >90% strut coverage at 3-months and >95% strut coverage at 12 months follow-up OCT.

### 13.4. Statistical Analysis Sites

Analysis will be undertaken by statisticians at the VA, Duke University and CRF.

### 13.5. Sample Size considerations

Previous studies have included similar number of patients in OCT follow-up of stent strut coverage.

We anticipate some patient attrition during the trial. The ideal assumption is to have a full sample 75 patients at baseline, 75 patients at 3-months and 75 patients at 12-month follow-up.

With attrition due to unforeseeable and clinically-driven events, we anticipate an inclusion of 75 patients at baseline, 65 patients at 3 months and 50 patients at 12-month follow-up.

## 14. SAFETY, DSMB AND COMPLAINT PROGRAM

Safety will be performed by IRB standards at each study site.

The central Jesse Brown VA site will perform electronic chart monitoring of a random sample of 10% of the study participants.

Electronic central monitoring will collect a random sample of:

- Informed consent forms
- Site Records
- Source Data (for verification and corroboration)

Safety of the subjects participating in this clinical trial will be monitored throughout the trial using the Adverse Event reporting process to identify real and potential safety issues.

### 14.1. Data Safety Monitoring Board (DSMB)

A Data and Safety Monitoring Board (DSMB) will be appointed to periodically review the conduct of the proposed trial for safety. The committee members will be cardiologists with experience in clinical research who will not be participating in the trial as investigators. Potential financial or intellectual conflicts of interest will be assessed prior to appointing the members. The DSMB will meet prior to the enrollment of the first subject to review the trial protocol, informed consent documents and plans for safety and data monitoring of the study. The DSMB will determine the risks and benefits to research subjects, protection and safety of the subjects and to offer suggestions for improving the study design. In addition, the DSMB will determine which data will be required for periodic review. The

DSMB will meet every 6 months to: determine adherence to study plan; review interim analysis, if applicable, and determine specific data to be analyzed; review protocol violations and deviations to assess adequacy of study; ensure documentation of informed consent; review enrollment followed eligibility criteria, enrollment numbers, visit compliance, or screening failure information; discuss investigator or key personnel changes; review completeness and quality of data collection forms; evaluate the aggregate analysis of adverse events/serious adverse events; review vital signs, clinical tests, etc.; and review confidentiality. At the end of each meeting the DSMB will give a recommendation to continue the trial unchanged, modify the protocols and/or consent form, or terminate the trial.

#### 14.2. Selection and Monitoring of Clinical Sites and Operators

In the selection of study investigators, the PI requires each physician to have adequate experience with investigational devices, demonstrate commitment to patient safety and consistency in adherence to study protocols.

Monitoring will be conducted by the PI and/or designee. These responsibilities include collecting and tracking data forms and instituting quality control measures for data entry verification and trial compliance.

### 15. MONITORING

Monitoring procedure will be performed based on the following FDA guidance and recommendations:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf>.

Centralized monitoring of the VA sites will be conducted for the SOLEMN trial.

- Data quality will be routinely monitored by a routine review of submitted data (CRF), angiograms, and OCT images. Follow-up on missing data, inconsistent data, data outliers and potential deviations will be provided to the sites when such occurrences are identified.
- Site performance metrics (enrollment numbers, high frequency of protocol deviations, delays in data submission) will be routinely performed.
- Completion of administrative and regulatory tasks will be performed, for example, compliance with local institutional review board (IRB) requirements or other appropriate local regulatory requirements.

#### 15.1. Monitoring of Critical Data and Processes



In order to provide highest level of protection of human subjects the following data and processes will be continuously monitored and feedback provided to the sites:

- Adherence to protocol eligibility criteria (inclusion/exclusion criteria)
- Ongoing evaluation, documentation and reporting of serious adverse events and unanticipated adverse device effects, subject deaths, subject withdrawals, especially when a withdrawal may be related to an adverse event
- Specifically, use of OCT in LM coronary artery will be continuously monitored to ascertain safety throughout the trial

With continuous monitoring, if a risk associated with the SOLEMN trial is identified, the principal investigator, study investigators and DSMB will act to remove the source of identified risk. Study monitoring will be adjusted accordingly in such instance to effectively oversee the identified risks.

#### 15.2. Communication of Centralized Monitoring

Written communication between the central monitoring site (Jesse Brown VA) and the local VA sites will be performed via encrypted government email systems only. Additionally, teleconferences, videoconferencing will be provided through secured VA government systems only.

#### 15.3. Clinical Events Committee (CEC)

The CEC is a group of 3 physicians with pertinent experience to review safety event data from the SOLEMN clinical study. This committee adjudicates individual AEs, which occur in the study. The CEC will also review and validate adverse events that occur over the course of the study and the subsequent classification of these adverse events as related to the device or procedure.

#### 15.4. Case report forms (CRF)

Case Report Forms will be collected via facsimile and sent to the central location at Jesse Brown VA Medical Center.

All information required and entered in the CRFs will be also available for later verification and confirmation in the VA electronic medical records (CPRS) should later confirmation be necessary.

The designated facsimile line for the SOLEMN trial only (312-569-7203) is in a locked and secured office with access only by the PI and Jesse Brown Research study personnel assigned to the SOLEMN protocol.

#### 15.5. Discontinuation Criteria for the Entire Trial

If the Sponsor, Data Safety and Monitoring Board, Clinical Events Committee, Regulatory Agency, and/or the Principal Investigator discover conditions during the study that indicate the investigation should be terminated for patient safety reasons, an appropriate schedule for termination will be instituted.

#### 15.6. Study Termination

If the study is terminated prior to the completion of expected enrollment for any reason, all participating centers will be notified within five working days. All patients already enrolled will continue to be followed for the planned course of study described in this protocol.

#### 15.7. Potential limitations

The main limitation of the proposed trial is absence of randomization and single arm design.

Additionally, due to logistical and financial considerations the sample size will be inadequate to determine the impact of Synergy on LM MACE.

We anticipate some patient attrition during the trial. The assumption is to have a full sample 75 patients at baseline, 75 patients at 3-months and 75 patients at 12-month follow-up.

### 16. ETHICAL ASPECTS OF THE PROPOSED RESEARCH

Angiographic follow-up of LM PCI has been routinely performed in the past in research and clinical settings.(27) ACC/AHA PCI guidelines consider use of intracoronary imaging guidance with IVUS a Class IIb recommendation, supporting the use of OCT as an intracoronary imaging method during the index procedure.(4)

Lastly, stent strut coverage after PCI has been assessed in numerous studies in the past supporting its safety and underlying the scientific rational for use.(11, 17, 41, 42)

Although participation in our study carries a small risk (related to performance of repeat invasive angiography and OCT we will make every effort to minimize it. To minimize the risk associated with angiography and OCT, patients at high risk for vascular access complications, allergy to contrast dye or other contraindications for repeat cardiac catheterization will be excluded from the study. Also patients will be monitored closely with clinic visits or phone follow-up as indicated in the protocol. To minimize the risk from cardiac catheterization and invasive OCT assessment, patients at high risk for complications, such as patients with peripheral vascular disease and renal failure, will also be excluded. All angiographic OCT imaging procedures will be performed by experienced, high-volume, interventional cardiologists.

## 17. DATA OWNERSHIP

Department of Veterans Affairs

## 18. INSTITUTIONAL REVIEW BOARD APPROVAL (IRB)

Local IRB will be obtained at each of the participating sites.

The local site investigators must obtain appropriate IRB approval before the study can be initiated. A copy of the written approval from the IRB and a copy of the approved informed consent form must be sent to the Jesse Brown VA Central Site.

### 18.1. Statement of Compliance

This study will be conducted in accordance with relevant parts of the Code of Federal Regulation (CFR), ISO 14155: Clinical Investigation of Medical Devices for Human Subjects-Good Clinical Practices, the relevant parts of the ICH Guidelines for Good Clinical Practices, ethical principles that have their origins in the Declaration of Helsinki, and pertinent individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB/EC and/or regulatory authority has been obtained, if appropriate. Any additional requirements imposed by the IRB/EC or regulatory authority shall be followed, if appropriate.

### 18.2. Signed Informed Consent

Signed informed consent forms (or copies) are to be maintained in the study file and must be available for verification by monitors or inspectors.

### 18.3. Subject Confidentiality

The coordinating Jesse Brown site and the local sites will maintain the confidentiality of the identity of subjects enrolled in the study and the information contained in their study records. The records will be made available as required for review by governing regulatory agency such as FDA and a reviewing IRB; the subject's identity will not be disclosed. All data used in the analysis and reporting of this evaluation will be used in a manner without identifiable reference to the subject.

### 18.4. Retention of Records by the Investigator

Investigators will retain records for a period of 3 years following the completion of the study, or as per local requirements, whatever is stricter.

## 19. IDE SUBMISSION

- IDE submission will be prepared in collaboration with:

**Alexandra Scrymgeour, MS, PharmD**

Acting Chief, Regulatory and Clinical Compliance Clinical Research  
Pharmacy Coordinating Center VA Cooperative Studies Program

Phone: (505)248-3203

Fax: (505)248-3205

Email: [Alexandra.Scrymgeour@va.gov](mailto:Alexandra.Scrymgeour@va.gov)

## 20. ROLE OF SPONSOR (JESSE BROWN VA COORDINATING CENTER)

As the sponsor of this clinical study, the central coordinating site at Jesse Brown VA Medical Center will hold the overall responsibility to conduct of the study.

### 20.1. General Duties

The central coordinating site at Jesse Brown VA Medical Center general duties consist of submitting applications and information to the FDA, obtaining regulatory and IRB approvals prior to allowing study commencement at selected sites, selecting investigators, ensuring proper investigational site monitoring and ensuring subject informed consent is obtained.

## 20.2. Selection of Investigators

The central coordinating site at Jesse Brown VA Medical Center will be involved in:

- Assuring selection of investigators qualified by training and experience
- Obtaining a signed investigator's agreement containing:
  - investigator's curriculum vitae
  - statement of investigator's relevant experience, including date, location, extent, and type of experience
  - if an investigator was involved in an investigation or other research that was terminated, an explanation of the circumstances that led to the termination
- statement of the investigator's commitment to conduct the investigation in accordance with the investigational plan and any conditions of approval imposed by the IRB or FDA
- ensure that the requirements for informed consent are met
- Providing investigators with the necessary information to conduct the investigation including, but not necessarily limited to:
  - the investigational plan
  - the report of prior investigations

## 20.3. Role of the Investigator

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical investigation plan, ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/EC, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following.

- Prior to beginning the study, sign the Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Prior to beginning the study, sign the Investigator Brochure Signature Page and Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the site team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.

- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event as applicable per the protocol and observed device deficiency.
- Report to sponsor, per the protocol requirements, all SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE.
- Report to the IRB/EC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE, if required by the national regulations or this protocol or by the IRB/EC, and supply Coordinating center with any additional requested information related to the safety reporting of a particular event.
- Maintain the device accountability records and control of the device, ensuring that the investigational device is used only by authorized/designated users and in accordance with this protocol and instructions/directions for use.
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the IRB/EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/EC requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- As applicable, provide the subject with necessary instructions on proper use, handling, storage, and return of the investigational device when it is used/operated by the subject.

- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

#### 20.4. Delegation of responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing appropriate training and adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

#### 20.5. Record Maintenance

The central coordinating site at Jesse Brown VA Medical Center will maintain copies of correspondence, data, shipment of studies, UADEs and other records related to this clinical study as required under local, VA and national regulations.

## 20.6. Communication with the FDA

The central coordinating site, Jesse Brown VA, will submit reports as required by the FDA regulations.

## 20.7. Prohibition of Promotion and Other Practices

The IDE regulations prohibit the promotion and commercialization of a device that has not been first cleared or approved for marketing by FDA. As indicated in the SOLEMN protocol, the SOLEMN trial is not designed to seek FDA approval for the Synergy stent for use in LM PCI nor it is designed to seek FDA approval for use of OCT in LM.

The central coordinating site, Jesse Brown VA, will actively monitor and prevent prolonging the SOLEMN trial beyond the point needed to collect data required to complete the trial.

## 20.8. Maintaining Records

The central coordinating site, Jesse Brown VA, shall maintain the following accurate, complete, and current records relating to the SOLEMN trial:

- Correspondence (including reports) with another sponsor, monitor, investigators, an IRB or FDA
- Records of investigational study images shipment
- Signed investigator agreements
- Adverse device effects (whether anticipated or unanticipated) and complaints
- Any other records that FDA requires by regulation or by specific requirement for a category of investigation or a particular investigation
- 

## 20.9. Submitting Reports

The central coordinating site, Jesse Brown VA shall prepare and submit the following complete, accurate, and timely reports:

- Unanticipated adverse device effects (with evaluation) to FDA, all IRBs, and investigators within 10 working days after notification by the investigator. Subsequent reports on the effect may be required by FDA.
- Withdrawal of IRB approval
- Withdrawal of FDA approval
- Annual progress report
- Final report



- Other reports as requested by the IRB or FDA

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## 22. APPENDIX A.

### 22.1. Case Report Forms

## 23. APPENDIX B.

### 23.1. CRF Proposal for OCT Analysis

## 24. APPENDIX C.

### 24.1. Jesse Brown VA Consent Form

## 25. APPENDIX D.

### 25.1. MACE Definitions

**Death** is defined as all cause death. Cardiac death is defined as any sudden death, death related to acute myocardial infarction, arrhythmia or congestive heart failure, death secondary to a cerebrovascular accident, or death directly related to PCI or CABG, even if the ultimate cause of death is not clearly a cardiac event (e.g., infection). Non-cardiac death is any death which is not clearly cardiac in etiology.

**Myocardial infarction** is defined in two ways, depending on whether or not it is PCI or CABG-related or a spontaneous event, as recently described in the literature.(43)

Spontaneous myocardial infarction (>48 hours after PCI or CABG):

Detection of rise and/or fall of cardiac biomarkers (CK-MB or troponin) with at least one value above the 99<sup>th</sup> percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:

- Symptoms of ischemia
- ECG changes indicative of new ischemia [new ST-T changes or new, persistent, non rate-related left bundle branch block (LBBB)]
- Development of pathological Q waves ( $\geq 0.03$  seconds in duration and  $\geq 1$  mm in depth) in  $\geq 2$  contiguous precordial leads or  $\geq 2$  adjacent limb leads of the ECG
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

PCI or CABG-related MI (<48 hours after PCI or CABG):

Elevation of the cardiac troponin value  $> 10 \times 99^{\text{th}}$  percentile of the URL in patients with a normal baseline reference level, or an increase of  $> 20\%$ , if the baseline values are elevated, but are stable or falling. In addition, at least one of the following:

- (i) new pathologic Q waves or new left bundle branch block
- (ii) angiographic documented new graft or new native coronary occlusion

- (iii) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormalities

is required.

**Stroke (cerebrovascular accident or CVA)** is the rapid onset of a focal or global neurological deficit. If the duration is <24 hours, the event is deemed a transient ischemic attack (TIA), except if an intervention is performed as defined below. If the duration is ≥24 hours, it is deemed a stroke. Stroke is subdivided as ischemic, hemorrhagic, or undetermined. Ischemic stroke refers to acute symptomatic episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of the central nervous system tissue. Hemorrhagic stroke is an acute symptomatic episode of focal or global cerebral or spinal dysfunction caused by nontraumatic intraparenchymal, intraventricular or subarachnoid hemorrhage. Undetermined stroke is one with insufficient information to allow categorization as either of the above two.

Stroke is diagnosed when the following criteria are met:

1. Rapid onset of a focal/global neurological deficit with at least one of the following:
  - Change in level of consciousness
  - Hemiplegia
  - Hemiparesis
  - Numbness or sensory loss affecting one side of the body
  - Dysphagia/aphasia
  - Hemianopia
  - Amaurosis fugax
  - Other new neurological sing(s)/symptom(s) consistent with stroke
2. Duration of focal/global neurological deficit is ≥24 hours, or it can be <24 hours if a therapeutic intervention is performed, brain imaging clearly documents a new hemorrhage or infarct, or the neurological deficit results in death.
3. Confirmation of the diagnosis by at least one of the following:
  - Neurology or neurosurgical specialist
  - Brain imaging (CT, MRI, or cerebral vessel angiography)
  - Lumbar puncture diagnostic of intracranial hemorrhage

**Urgent revascularization** is defined as an unplanned hospitalization for an acute coronary syndrome which results in revascularization during the hospitalization.

**Repeat revascularization** is defined as any unplanned (elective or urgent) revascularization, whether PCI or CABG. Planned staged PCI procedures do not qualify.



**Bleeding** is defined as per the Bleeding Academic Research Consortium (BARC).(44) Other descriptions of bleeding, such as TIMI, may be applied as well.

**Stent thrombosis** is defined as per the Academic Research Consortium.(45)

**Rehospitalization** is defined as a hospital stay of >24 hours

## 25.2. Safety Definition

One-month LM Synergy stent safety is defined as a composite of cardiac death and target vessel MI at 1 month after index PCI.

**Cardiac death.** Any death due to proximate cardiac cause (e.g., MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, all procedure-related deaths including those related to concomitant treatment.

**Target vessel MI** will be defined as all as MIs that occur in the distribution of the LM, LAD, and LCX coronary arteries.